

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application Number : 10/581,835 Confirmation No. 8539
Applicant : Tor Kihlberg
Filed : June 5, 2006
Title : METHOD AND APPARATUS FOR SYNTHESIS OF [¹¹C]
PHOSGENE USING CONCENTRATED [¹¹C] CARBON
MONOXIDE WITH UV LIGHT (*As Amended*)
TC/Art Unit : 1618
Examiner: : Melissa Jean Perreira
Docket No. : PH0381
Customer No. : **36335**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF PROF. BENGT LÅNGSTRÖM UNDER 37 C.F.R. § 1.132

I, Bengt Långström, do hereby declare that:

1. I am named inventor in the captioned application.
2. I am presently a Professor Emeritus at Uppsala University in Sweden, in the Department of Biochemistry and Organic Chemistry. I was a professor in chemistry at Uppsala University from 1989 to 2010. I am also a member of the Faculty of Medicine at Imperial College in London, UK, in the Neuropsychopharmacology Unit Centre for Pharmacology and Therapeutics Division of Experimental Medicine. I am also affiliated with the Odense University Hospital, in Denmark and the Department of Nuclear Medicine, PET & Cyclotron Unit at the University of Southern Denmark, Odense.
3. I received my B.S. in 1968, M.S. in 1970, and Ph.D. in 1980, all from Uppsala University.
4. I was Chief Scientific Officer at Imanet (Amersham Health), which later became part of GE Healthcare, from 2002 to 2009. Before that, I was head of R&D at Uppsala Imanet

from 2002 to 2006 and Managing Director of Uppsala Research Imaging Solutions (URIS) AB in 2002. Prior to my affiliation with URIS, I was Director of Uppsala University PET Centre from 1990 to 2002. From 1993 to 1998 I was also Director of the “Subfemtomole Biorecognition Project”, RDC of Japan.

5. I have been performing research in the area of positron emission tomography (PET) since 1977. My focus has been primarily on the generation and incorporation of the ^{11}C -isotope into organic and biological compounds. My work in this field dates back as far as 1985. In sum, I am at least one of ordinary skill in the art.
6. I have reviewed the claims that are currently before the examiner in the captioned application. I understand that the invention is generally directed to a method for synthesizing high specific activity carbon-isotope labeled phosgene from carbon-isotope monoxide and Cl_2 gas in a closed reaction chamber. The labeled phosgene is generated by irradiating the carbon-isotope monoxide and Cl_2 gas mixture with UV-light. I have also reviewed the poster presented by Oleksiy Itsenko and Tor Kihlberg, on September 10, 2010 at the 2010 World Molecular Imaging Congress in Kyoto, Japan. A copy of the poster and an abstract, are provided herewith.
7. I have reviewed and analyzed the non-final Office Action dated March 31, 2011 (“the Office Action”), which issued in connection with the captioned application. In the Office Action, claims 1-5 and 7 stand rejected as being unpatentable over the teachings of Diksic *et al.* (*Int. J. Nucl. Med. Biol.* 9: 283-285 (1982)) in combination with several references, including Suzuki *et al.* (EP0282703B1); Shiba *et al.* (US 4,458,302); and Gascard *et al.*, (*J. Phys. E. Sci. Instrum.* 15: 627-628 (1982)).
8. Briefly, Diksic discloses a continuous flow method for synthesizing [^{11}C]phosgene, where ^{11}CO and Cl_2 are irradiated with UV-light as the gases continuously flow through a quartz spiral, thereby producing the labeled phosgene. Diksic reports a specific activity for the [^{11}C]phosgene of 1.48 TBq/mmol (40 Ci/mmol). Diksic at 284, right-hand column. Diksic also reports that this value is “ 10^5 lower than the theoretical specific

activity of $^{11}\text{COCl}_2$.” *Id.* Finally, Diksic attributes such a large departure from the theoretical specific activity to the chlorine that he used in his experiments, “since the specific activity of ^{11}C]phosgene is at least 2.5×10^3 times lower than the specific activity of ^{11}C]carbon monoxide.” *Id.*

9. The claimed method of making carbon-isotope labeled phosgene, including ^{11}C]phosgene, significantly differs from Diksic’s method for a number of reasons. First, the claimed method for synthesizing labeled phosgene involves the batch-wise synthesis of the compound. The fact that the claimed method requires a “reaction chamber” implies that the system used to synthesize the labeled phosgene is a closed reaction system, in contrast to Diksic’s continuous flow system. Second, the volumes of carbon-isotope monoxide enriched gas-mixture and Cl_2 gas used in the claimed method are minute (*e.g.*, in the order of microliters) relative to the amounts of gas(es) Diksic uses. For example, in his experiments, Diksic flows Cl_2 gas through his system at a rate of 10 mL/min and ^{11}C]carbon monoxide in carrier gas (*i.e.*, nitrogen gas) at a rate of 20-60 mL/min. Diksic at 283, right-hand column. A typical synthesis run for Diksic appears to be ten minutes. Diksic at 284, left-hand column. Accordingly, in one synthesis run, Diksic could use 100 mL of Cl_2 gas and 200-600 mL of ^{11}C]carbon monoxide in carrier gas.
10. Since Diksic uses such large volumes of gases, it is no wonder that he obtains ^{11}C]phosgene with a low specific activity that is 100,000 times lower than the theoretical specific activity. The use of such large volumes of gases leads to significant isotopic dilution by, *e.g.*, “cold” phosgene present in the Cl_2 gas. Diksic suspects as much as evidenced by his statement on page 284, right-hand column: “[w]e suspect chlorine, even though we have used research purity chlorine (99.5%), since the specific activity of ^{11}C]phosgene is at least 2.5×10^3 times lower than the specific activity of ^{11}C]carbon monoxide.”
11. In contrast, the claimed method produces ^{11}C]phosgene with significantly higher specific activity that is at least one order of magnitude higher than the specific activity of Diksic’s ^{11}C]phosgene. For example, the claimed method produces ^{11}C]phosgene with a

surprisingly high radioactivity of 200 GBq/ μ mol, which amounts to 200 TBq/mmol, and a decay-corrected radiochemical yield of 70–85%. These data and findings were presented by Oleksiy Itsenko and Tor Kihlberg (a named inventor in the captioned application), on September 10, 2010 at the 2010 World Molecular Imaging Congress in Kyoto, Japan. Moreover, these results are in agreement with the high specific radioactivity of compounds obtained using the ^{11}C -carbon monoxide produced in a similar reactor system. *See, e.g.*, US2009/0297445.

12. The high radioactivity and radiochemical yield are a direct result of a significant reduction in isotopic dilution during the labelling synthesis, to the point that it becomes negligible. Such a significant reduction in isotopic dilution is, in turn, attributed to the use of small reaction volumes/amounts of reactants.
13. It is noteworthy that Diksic considers his method as one that produces “high specific activity (no carrier added) [^{11}C]phosgene.” Diksic at 283, right-hand column. Accordingly, those of skill in the art would not be motivated to change Diksic’s continuous flow apparatus because, according to him, such an apparatus already produces “high specific activity” [^{11}C]phosgene. Accordingly, those of skill in the art would not be motivated to abandon Diksic’s continuous flow method for synthesizing [^{11}C]phosgene in favor of the claimed method, which uses a closed reaction system. In other words, it would not have been obvious to arrive at the claimed method for making [^{11}C]phosgene based on Diksic’s disclosure.

14. I declare further that all statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further, these statements were made with the knowledge, that willful false statement and the like thereof made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and such willful false statements may jeopardize the validity of the above-named application or any patent issuing thereon.

Respectfully submitted,



Date: Uppsala 2011 08 16

By:

Bengt Långström